Bilberry Supplementation on Metabolic and Cardiovascular Disease Risk

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Bilberry (Vaccinium myrtillus L.) is one of the richest natural sources of anthocyanins which give berries their red/purple/blue coloration. Anthocyanins are powerful antioxidants and are reported to play an important role in the prevention of metabolic disease and CVD as well as cancer and other conditions.

Keywords: bilberry ; antioxidant ; anti-inflammatory ; cardiovascular disease ; hypoglycemic effect ; type 2 diabetes

1. Introduction

Metabolic syndrome is a cluster of conditions that includes insulin resistance, central obesity, hypertension, elevated triglycerides, decreased high-density lipoprotein (HDL) cholesterol and low-grade chronic inflammation [1], increasing the risk of developing cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [2]. Increased oxidative stress is one of the triggers of chronic inflammation [1]. Atherosclerosis, the main underlying cause of CVD, is associated with an ongoing inflammatory response and oxidative processes that lead to the modification of atherogenic lipoproteins [3]. T2DM is considered to be associated with increased oxidative stress, inflammation, and dyslipidemia, which may play a significant role in the development of cardiovascular complications, cancer and vision loss through cataracts and retinopathy [4][5][6][7][8].

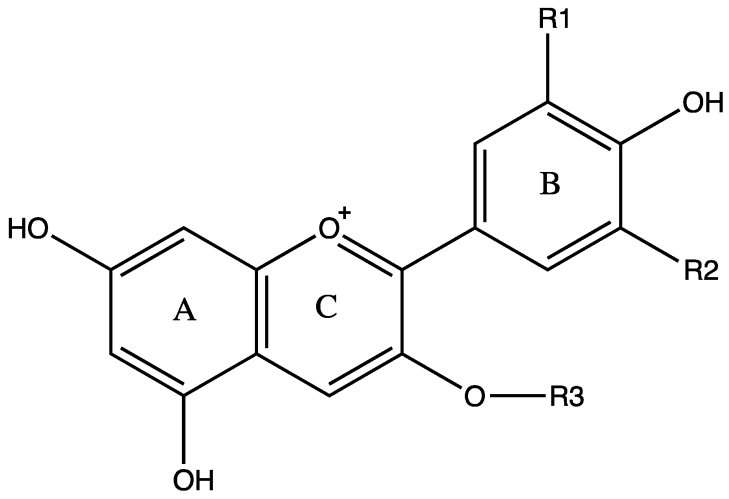
The management of the major risk factors of metabolic syndrome with conventional therapies is partially effective in reducing cardiovascular events and progression to obesity and T2DM. Recently, there is growing awareness of the importance of dietary factors as a major determinant of metabolic syndrome. Increased consumption of fruits and vegetables has been associated with a decreased risk of metabolic syndrome and CVD. Polyphenolics present in fruits and vegetables have been shown to provide diverse cardioprotective effects [9]. Berries, particularly bilberry (*Vaccinium myrtillus L.*) which belongs to the heather family (Ericaceae), have a very high content of anthocyanins, which are polyphenolic compounds that give berries their red/purple/blue coloration [8][10]. Bilberry is one of the richest natural sources of anthocyanins and their anthocyanin content is higher than that of other types of berries, such as strawberry, cranberry, elderberry, sour cherry, and raspberry [11][12][13][14]. A total of 15 different types of anthocyanins have been identified in bilberry fruit, juice, and extract. In addition to anthocyanins, bilberry also contains flavonols (quercetin and catechins), tannins and phenolic acids [11].

Anthocyanins are powerful antioxidants that can neutralize free radicals [15]. In addition to their antioxidant effects, anthocyanins have been reported to suppress lipid peroxidation, stabilize DNA, modify adipocyte gene expression, improve insulin secretion and sensitivity, and have anti-carcinogenic, anti-inflammatory, and antibacterial effects [12][16][17]. Although the potential value of bilberry in the treatment or prevention of conditions associated with inflammation, dyslipidemia, diabetes and CVD has been recognized, strong evidence from controlled human supplementation studies in T2DM patients is lacking, and data from in vitro studies and animal studies cannot always be extrapolated to the clinical setting [18].

2. Chemical Structure, Distribution and Bioavailability of Anthocyanins

Anthocyanins are water-soluble polyphenolic vascular pigments that give berries their bright coloration [8][10]. The relative color of anthocyanins in aqueous solution is pH dependent. In acidic conditions, anthocyanins appear as red, but turn blue when the pH increases and finally become colorless at very high pH [19]. In terms of chemical structure, anthocyanins are glycosylated, polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrylium (flavylium cation) that contain two phenyl rings (A and B) separated by a hetero-cyclic (C) ring [20]. Anthocyanins usually contain a single glucoside unit but vary in the number of hydroxyl groups, the nature and number of sugars attached to the molecule, the position of the attachment, and the nature and number of aliphatic or aromatic acids attached to sugars in the molecule [16]. The main anthocyanins

found in bilberry in decreasing contents are delphinidins (15.17%), cyanidins (8.36%), petunidins (6.64%), malvidins (5.43%) and peonidins (1.87%) [11][20] (**Figure 1**). Common sugars that attach to anthocyanins include glucose (Glu), galactose (Gal), arabinose (Ara), rutinose (Rut), rhamnose (Rham), and xylose (Xyl) and these sugars are bound as mono-, di-, or trisaccharide forms [21]. Anthocyanins have powerful antioxidant properties, and the content of anthocyanin directly correlates with the antioxidant activity of plants [11][22][23][24].



Anthocyanin (% in Content in Bilberry)	R1	R2	λ_{max} (nm) *	
			R3=H	R3=gluc
Delphinidin (15.17%)	OH	OH	546	541
Cyanidin (8.36%)	OH	H	535	530
Petunidin (6.64%)	OH	OCH_3	543	540
Malvidin (5.43%)	OCH_3	OCH_3	542	538
Peonidin (1.87%)	OCH_3	H	532	528

* In methanol with 0.01% HCl.

Figure 1. Structures of the main anthocyanin-3-*O*-glucosides found in bilberry and respective wavelength at the maximum absorption in the visible region (λ_{max}). Note that anthocyanins have characteristic colors, but the color of anthocyanins can change with the pH of the solution [11][20].

The usual dietary intake of anthocyanins is approximately 200 mg daily [25]. Anthocyanins, unlike other polyphenolic flavonoids, are absorbed rapidly in the intact glycosidic form and do not undergo extensive metabolism [26]. Anthocyanins can be detected in the plasma 6–20 min following consumption and plasma levels reach maximum after 15 to 60 min [27]. In rats, anthocyanins are absorbed from the stomach and also from the small intestine, and the absorption efficiency varies depending on the structure of the anthocyanins. Some anthocyanins can reach the large intestine in significant amounts and undergo extensive decomposition catalyzed by colonic microbiota [21]. Absorption of anthocyanins through the gastric wall typically ranged from 11% for malvidin-3-glucoside to 22% for cyanidin-3-glucoside [13]. Anthocyanins have relatively low oral bioavailability and are capable of crossing the blood–brain barrier [28]. In animal studies, the systemic bioavailability of anthocyanins was estimated to be 0.26–1.8% [21][29][30][31][32]. In mice fed with a diet containing 0.5% bilberry extract for two weeks, plasma levels of anthocyanins reached a maximum of 0.26 µmol/L and anthocyanins were detected in the liver, kidney, testes, and lung but not the brain, heart, muscle, eyes, or white fat, suggesting that bilberry anthocyanins are absorbed and distributed in specific organs [33]. It has been reported that urinary excretion of anthocyanins was very low (0.005–0.1% of intake), suggesting pronounced biliary excretion or extensive metabolism of the compounds [34]. In humans, anthocyanins are cleared rapidly and after 6 h, very little is detected in the plasma [35]. Several studies have demonstrated improved plasma antioxidant status after consumption of berries [36][37], suggesting that berry components with antioxidant activity are bioavailable.

3. Beneficial Effects of Bilberries

Considerable attention has focused on the health benefits of dietary polyphenols, including anthocyanins. In vitro experiments, animal studies and clinical trials suggested that consumption of anthocyanins results in antioxidant, anti-

inflammatory, anti-diabetic, anti-dyslipidemic and anti-hypertensive effects and the health benefits are associated with their potential antioxidant effect. **Table 1** lists several of the important clinical studies that have investigated the health benefits of bilberry supplementation in healthy subjects or in subjects with increased CVD risk.

Table 1. Intervention studies of bilberry. LDL: low-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; IL: interleukin; LPS: lipopolysaccharide; NF-κB: nuclear factor-κB; sVCAM-1: soluble vascular cell adhesion molecule-1; HDL: high-density lipoprotein; CETP: cholesteryl ester transfer protein; CVD: cardiovascular disease; T2DM: type 2 diabetes mellitus; CADP-CT: closing time in platelet function analyzer with collagen and ADP; FMD: flow-mediated dilation; cGMP: cyclic guanosine monophosphate.

Authors	Type of Study	Subjects	Interventions	Findings
Antioxidant effect				
Marniemi et al. [38]	Randomized controlled trial	60 healthy volunteers	100 g deep-frozen berries (bilberries, lingonberries, or blackcurrants) daily for 8 weeks; 240 g berries in postprandial study; or 500 g calcium gluconate	Increased serum ascorbate, slight decrease in LDL oxidation, slight increase in serum antioxidant capacity in berry group; decreased LDL oxidation in postprandial study
Duthie et al. [18]	Randomized controlled trial	20 healthy volunteers	750 mL/day of cranberry juice (Ocean Spray Cranberry Select) or placebo drink (natural mineral water with strawberry flavor + sucrose (9 g/100mL)) for 2 weeks	No effect on blood or cellular antioxidant status, lipid status, or oxidative DNA damage between groups
Karlsen et al. [39]	Randomized controlled trial	62 volunteers with increased risk of CVD	330 mL/day bilberry juice (Corona Safteri, Rotvoll, Norway) or water for 4 weeks	No effect on antioxidant status or oxidative stress
Arevstrom et al. [40]	Randomized controlled trial	50 patients who were within 24 h of percutaneous coronary intervention	Bilberry powder (40 g/d, equivalent to 480 g fresh bilberries) or no supplementation over 8 weeks	Reduced total and LDL cholesterol compared to baseline; no difference in total and LDL cholesterol between groups
Anti-inflammatory effect				
Kolehmainen et al. [41]	Randomized controlled trial	27 volunteers with features of metabolic syndrome	400 g/day fresh bilberries or habitual diet for 8 weeks	Reduced hsCRP, IL-6, IL-12, and LPS concentrations
Karlsen et al. [39]	Randomized controlled trial	62 volunteers with increased risk of CVD	330 mL/day bilberry juice (Corona Safteri, Rotvoll, Norway) or water for 4 weeks	Modulate NF-κB relatedinflammatory markers

Authors	Type of Study	Subjects	Interventions	Findings
Karlsen et al. [42]	Randomized controlled trial	120 healthy volunteers	300 mg/day Medox (with purified anthocyanins isolated from bilberries and blackcurrant), or placebo (maltodextrin) capsules for 3 weeks	Decreased NF-kB related pro-inflammatory chemokines, cytokines, and mediators of inflammatory responses
Zhu et al. [43]	Randomized placebo controlled, double-blinded trial	150 hypercholesterolemia subjects	Anthocyanins (320 mg/d) purified from bilberry and blackcurrant, or placebo for 24 weeks	Decreased hsCRP, sVCAM-1, IL-1b and LDL cholesterol and increased HDL cholesterol
Freese et al. [44]	Randomized controlled trial	96 healthy volunteers	Experimental diets either poor or rich in vegetables, berries and apple, and either richin linoleic acid or oleic acid for 6 weeks	No effect on platelet activation or inflammation markers
Hypoglycemic effect				
Hoggard et al. [45]	Randomized placebo controlled, double-blinded cross-over study	8 volunteers with T2DM controlled by diet and lifestyle	0.47 g bilberry extract (36% (w/w) anthocyanins) capsule or placebo	Decreased postprandial glycemia and insulin level
Qin et al. [46]	Randomized placebo controlled, double-blinded trial	120 overweight dyslipidemic subjects	160 mg anthocyanins twice daily or placebo for 12 weeks	No difference in glucose levels between groups
Effects on dyslipidemia				
Qin et al. [46]	Randomized placebo controlled, double-blinded trial	120 overweight dyslipidemic subjects	160 mg anthocyanins twice daily or placebo for 12 weeks	Decreased LDL cholesterol and increased HDL cholesterol and inhibited CETP

Authors	Type of Study	Subjects	Interventions	Findings
Erlund et al. [47]	Randomized, placebo controlled, single-blind, trial	71 volunteers with at least one CV risk factor	100 g whole bilberries and 50 g lingonberries one every other day, and blackcurrant or strawberry purée and cold-pressed chokeberry and raspberry juice on alternative day, or placebo (sugar water, sweet semolina porridge, sweet rice porridge and marmalade sweets) for 8 weeks	Reduced blood pressure, increased HDL cholesterol and prolonged PFA-100 CTs (CADP-CT)
Zhu et al. [48]	Randomized controlled, double-blinded trial	150 hypercholesterolemic subjects	320 mg/d anthocyanins purified from bilberry and blackcurrant, or placebo for 12 weeks	Increased FMD, cGMP, and HDL cholesterol, and decreased serum sVCAM-1 and LDL cholesterol
Zhu et al. [49]	Randomized placebo-controlled, double-blind, parallel study	122 hypercholesterolemic subjects	320 mg/d anthocyanins purified from bilberry and blackcurrant, or placebo for 24 weeks	Increased HDL cholesterol and decreased LDL cholesterol

4. Adverse Effects of Bilberry

Bilberry has been recognized as a Class 1 herb by the American Herbal Products Association, meaning it is considered safe to consume when used appropriately [11]. An open pilot trial with bilberry preparation has included safety, tolerability, side effects and patient satisfaction in the analysis and reported no serious clinical adverse events nor alternations in the safety laboratory parameters [50]. No known adverse effect of bilberry and bilberry extract has been reported in other studies [39][40][45]. Due to the anti-platelet activity of bilberry, patients taking a chronic high dose of concentrated bilberry extract in combination with anti-platelet drugs should be monitored for hemorrhagic disorders. Bilberry has no known interactions with other drugs.

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